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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,689	WILLIAMS, JOHN G.K.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *4-17,20,21,24,25 and 27-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,18,19,22,23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-28, species of claims 3, 22, 23 and 26) in the reply filed on November 22, 2006 is acknowledged. The traversal is on the ground(s) that there is no undue burden of search. This is not found persuasive because Applicant did not provide any reasons why the search for the product and process claims is not burdensome.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 4-17, 20, 21, 24, 25 and 27-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species and inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 22, 2006.

3. Claims 1-3, 18, 19, 22, 23 and 26 will be examined.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on December 27, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Interpretation

5. The term "attachment complex" has not been defined by Applicant, therefore it is considered as any molecule. Further, the term "polymerase has an attachment complex" is interpreted as "polymerase comprises an attachment complex" and the attachment complex may be covalently or non-covalently linked to the polymerase.

6. Applicant did not define the term "anchor", therefore it is considered as any molecule.

7. Applicant did not define the term "irreversible association", therefore, any association is considered as irreversible, provided the time scale or topological constraints.

8. Applicant defined the term "processivity index" on page 7, [0038], as the number of nucleotides sequenced divided by the number of nucleotides in the template.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 18, 19, 22, 23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-3, 18, 19, 22, 23 and 26 are broadly drawn to a polymerase-nucleic acid complex comprising a target nucleic acid and a nucleic acid polymerase, where the polymerase has an attachment complex comprising at least one anchor which irreversibly associates the target nucleic acid with the polymerase to increase the processivity index. However, as will be further discussed, there is no support in the specification and prior art for the claimed invention. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has no working examples of a polymerase-target nucleic acid complex in which a polymerase comprises an attachment complex with at least one anchor which irreversibly associates the nucleic acid with the polymerase.

Guidance in the Specification.

The specification provides no evidence that a complex between a nucleic acid target and a polymerase which has an anchor irreversibly associating nucleic acid with the polymerase would be both functional as a polymerase and possess increased processivity. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification (page 11, 12, [0050], [0051]; Fig. 2) discloses an idea of a 9 Degrees North DNA polymerase that has two 21-amino acid sequences inserted at positions K53 and K229 of the polymerase. These two peptides are attached to the solid support. Applicant point to a structural model 1QHT.pdb, however, this is a structural model of the 9 Degrees North DNA polymerase, not of the construct shown in Figure 2.

Applicant did not show any evidence that the polymerase modified in such a way functions as a polymerase, i.e., that no major structural changes are introduced by the modifications

described. Further, it is not clear how a linear DNA molecule can be possible irreversibly associated with the polymerase. In the case of a double-stranded DNA molecule, Applicant did not show that large circular molecules could be sequenced without an addition of proteins like a helicase, which relieve the torsional stress. Without such molecules present in the reaction the polymerase would need to dissociate from the DNA, thus, the processivity would not increase. Applicant also did not show that the proposed change to the polymerase structure does indeed increase processivity. Finally, in view of the fact that there are hundreds of different polymerases, both RNA-dependent and DNA-dependent, with different target specificities and structures, the guidance in the specification is insufficient to make and use the claimed invention.

The unpredictability of the art and the state of the prior art

The specification recites one proposed change to a structure of a 9 Degree North DNA polymerase, and proposes that any DNA polymerase can be used for such purpose (page 12, [0052]-[0054]. However, as can be seen from the prior art, there is a great deal of uncertainty in terms of the influence of mutations on the properties of nucleic acid polymerases, because of the way they interact with their targets. To start with, let us look at some structures of DNA polymerases. In a review of Arnold et al. (Current Opinion in Structural Biology, vol. 5, pp. 27-38, 1995), structures of several DNA- and RNA-dependent polymerases are compared (page 27, first paragraph). They all contain structurally similar overall fold, resembling a right hand, with domains named "fingers", "palm" and "thumb" (Fig. 1). There are extensive contacts formed between the thumb domain and/or finger domains of these polymerases with substrate nucleic acid (page 27, second paragraph; page 29, second paragraph; page 31, third and fifth paragraph; page 32, first paragraph). The structures of RB69 DNA polymerase complexed to a primer-template (Franklin et al., Cell, vol.

105, pp. 657-667, 2001) and the 9 Degree North DNA polymerase (Rodriguez et al., J. Mol. Biol., vol. 299, pp. 447-462, 2000) show an overall similar fold and structural domains.

These structures are not static, though. As evidenced by Patel et al. (J. Mol. Biol., vol. 308, pp. 823-837, 2001), DNA polymerases undergo conformational changes during the process of DNA synthesis, which consists of polymerase binding with template-primer (TP), binding of dNTP to the complex, a nucleophilic attack resulting in phosphodiester bond formation and release of pyrophosphate (page 827, second paragraph). The conformational changes occur during the DNA binding step, when the thumb domain wraps around the DNA (page 827, second and third paragraphs); during the dNTP binding step, where the finger domain elements rotate towards the 3' primer terminus, resulting in a "closed" structure", the template base rotates back into the helix axis and the bae portion of the incoming nucleotide forms a base-pair with the template base and the triphosphate forms metal-mediated ionic interactions with amino acid residues of the active site (page 827, second and last paragraph; page 828, first paragraph; Fig. 5, 6); during PPi release and subsequent translocation, when the polymerase adopts an "open" conformation (page 827, second paragraph; page 831, last paragraph; page 832, first paragraph). Therefore, the overall picture is of extensive conformational changes involving large parts of the polymerase structure.

A similar situation was observed when the structures of RNA plymerase II, which is involved in mRNA transcription in eucaryotes, were examined (Gnatt, Biochim. Biophys. Acta, vol. 1577, pp. 175-190, 2002). A high-resolution structure of an elongation complex shows a large cleft bordered by a "clamp", "wall" and second cleft border, with two "jaws" extending from the first and second cleft borders (Fig. 3; page 180, last paragraph; page 181, paragraphs 1-4). The clamp was found to undergo conformational change upon target binding involving a shift of some residues

by as much as 30 A (Fig. 6; page 182, last paragraph; page 183). As stated by Gnatt et al. (page 183, second paragraph):

"The enzyme prevents nucleic acid from escape, increasing processivity, yet too tight a "grip" on RNA/DNA would prevent efficient elongation of the RNA chain. One could picture RNAP transcribing very long megabase transcripts such as dystrophin, which would require securing the template from release despite hubdreds of thousands of bases that are to be synthesized."

Finally, as to the role of mutations in polymerase processivity, the emerging picture is that mutations in different parts of the protein affect its processivity. Gross et al. (J. Mol. Biol., vol. 228, pp. 488-505, 1992) examined properties of mutants of T7 RNA polymerase obtained by linker insertion mutagenesis (Abstract; Table 1). For example, an insertion of two amino acids at the residue 881 at the very C-terminus of the proteins results in a greatly reduced processivity (page 503, paragraphs 1-3). Pandey et al. (Eur. J. Biochem., vol. 214, pp. 59-65, 1993) describe the effects of mutating the Arg682 residue of DNA pol I from E. coli. Mutating this residue to either alanine or lysine resulted in reduced enzyme processivity, even though Arg682 is thought to interact directly with the incoming dNTP (Abstract; page 62, paragraphs 3, 4; page 63; page 64, paragraphs 1-4; Fig. 6 and 7). Spacciapoli et al. (J. Biol. Chem., vol. 269, pp. 438-446, 1994) found that the A737V mutation in the bacteriophage T4 DNA polymerase decreased its processivity as a polymerase and increased its processivity as a 3'-> 5' exonuclease (Abstract; page 440, fifth paragraph; Fig. 3), and that the processivity can be restored using L771F mutation (Abstract; page 440, sixth paragraph; Fig. 3).

In conclusion, it is clear from the evidence presented above that it is not possible to predict a priori a result of structural changes introduced into a polymerase. Thus, addition of two peptides to

the polymerase residues coupled with polymerase immobilization using these peptides (or other molecules), may lead to a totally inactive polymerase.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to make polymerase-nucleic acid complexes in which nucleic acids are irreversibly associated with the polymerase and in which the polymerase has increased processivity. The project would involve testing attachment complexes comprising anchor molecules which can be of any kind in association with the polymerase which could be either covalent or non-covalent and testing such complexes with all possible polymerases. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the structure of the polymerase determines its function and where the effect of structural changes cannot be predicted a priori, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the unpredictability of mutations on the polymerase structure and function. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

10. Note: the rejection presented below does not contradict the rejection of claims 1-3, 18, 19, 22, 23 and 26 under 35 U.S.C. 112, first paragraph, enablement, presented above, in view of the broad interpretation of claim language

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-3, 18, 19 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Yao et al. (Genes to Cells, vol. 1, pp. 101-113, 1996).

Regarding claim 1, Yao et al. teach a polymerase-nucleic acid complex, where the polymerase comprises a gp45 clamp or a PCNA clamp (=attachment complex), which irreversibly associates the polymerase with the nucleic acid to increase processivity (page 111, last paragraph; page 112, paragraphs 1, 2 and 4; Abstract; page 104, third-fifth paragraphs; page 105, first paragraph; Fig. 3).

Regarding claim 2, Yao et al. teach a complex with a primer (page 111, last paragraph; page 112, first paragraph; page 104, third paragraph).

Regarding claim 3, Yao et al. teach that gp45 and PCNA have three subunits (= anchors) (page 101, first paragraph; page 102, first paragraph).

Regarding claim 18, Yao et al. teach circular DNA (page 111, last paragraph; page 112, first paragraph; page 104, third paragraph).

Regarding claim 19, Yao et al. teach that the circular DNA molecules were nicked (page 111, fifth paragraph), therefore they were inherently amplified by strand displacement.

Regarding claim 26, Yao et al. teach increased processivity of the polymerases with their processivity clamps (Abstract), and since the processivity depends of on the reaction conditions and a specific template, it is inherent that the processivity of the polymerase with the clamp would be at least 0.5 with respect to the polymerase without the clamp.

13. No references were found teaching or suggesting claims 22 and 23, but they are rejected for reasons given above.

14. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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12/21/06